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TPA-induced apoptosis in myeloid leukemia cells

Despite recent advances in the development of chemotherapy and bone marrow transplantation regimens, the overall clinical outcome for acute myeloid leukemia (a form of leukemia) remains dismal. The long-term goal of the present research project is to develop effective strategies for the treatment of acute myeloid leukemia. Effective treatment and the overcoming of resistance in this form of leukemia may be achieved by using suitable combinations of anticancer agents. However, most current chemotherapy regimens consist of empirically designed combinations. We propose to develop effective combination therapies for the treatment of acute myeloid leukemia based on studies of interaction of anticancer agents at molecular level. Our preliminary studies as well as studies from other investigators showed that a naturally occurred compound TPA (a phorbol ester) induces leukemia cell death (named apoptosis). We also found that proteins such as protein kinase C and a nuclear transcription factor (NF- κ B) are involved in the TPA-induced apoptosis and resistance in these leukemia cells. In the present proposal, we plan to design and test combinations of TPA and inhibitors of NF- κ B for enhancing apoptosis and overcoming resistance in myeloid leukemia cells. These studies may lead to the development of more effective treatment and the overcoming of resistance in myeloid leukemia patients.

Our laboratory in collaboration with colleagues in China have demonstrated that administration of TPA alone, or in combination with other anticancer agents resulted in remissions in some patients with acute myeloid leukemia who failed to respond to other anticancer drugs. Dr. Roger Strair (Cancer Institute of New Jersey) obtained appropriate FDA and institutional approvals, and he has initiated a Phase I clinical trial in leukemia patients in New Brunswick, New Jersey in collaboration with our laboratory. Because of our studies with TPA at Rutgers University and the clinical studies with TPA at the Cancer Institute of New Jersey, our state has pioneered in research for developing TPA as a potential new anticancer drug. The present research proposal will strengthen the leadership of New Jersey in this research field. The successful development of TPA-based combination therapy will provide an opportunity for the treatment of critical ill myeloid leukemia patients in New Jersey who fail to respond to other therapeutic regimens.